REMARKS

Reconsideration and further examination of this application is hereby requested. Claims 1-44 are cancelled. Claims 45-47 are currently pending in the application. Claims 48-54 are newly added.

No new matter has been entered.

I. OBVIOUSNESS REJECTIONS

Claims 45-47 have been rejected under 35 U.S.C. § 103(a) as being obvious over *Debouck* (Nature Genetics Supplement, Vol. 2 pages 48-50, January 1999) in view of *Lillicrap et. al* (US 6351632) or *Aguirre* (US 6201114) and in further view of *Pirson* (GenBank Accession Number X95367, October 1996) and *Yokota* (GenBank Accession Number AB0008451, October 1997) and *Nakamura* et al. (GenBank Accession Number AB012918, October 1999) and *Van Leeuwen el al.* (GenBank Accession Number L371072, February 1997) and *Kobayashi et al.* (GenBank Accession Number AB028042, November 1999) and *Somberg* (GenBank Accession Number U28141, June 1995) and *Kobayashi* (GenBank Accession Number D84397, June 1999) and *Manning et al.* (GenBank Accession Number L31625, April 1994) and *Puel et al.* (GenBank Accession Number Af045016, February 1998) and *Ortiz-Garcia et al.* (GenBank Accession Number AF021873, July 1999).

These rejections are respectfully traversed based on the

following arguments.

A. THE EXAMINER HAS FAILED TO ESTABLISH A *PRIMA FACIE* CASE OF OBVIOUSNESS FOR CLAIM 45-47.

In order for a patent claim to be obvious, the prior art must teach or suggest all the limitations of that claim. "In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness." In re Rijckaert, 9 F.3d 1531, 1532, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993).

Independent claim 47 (as amended) recites the limitation of "an array comprising at least 10 nucleic acid molecules wherein the 10 nucleic acid molecules are SEQ.ID Nos.: 115-124. SEQ ID. Nos.: 115-124 hybridize respectively to at least a portion of the genes coding for c-myc, c-erbB2, catalse, p53, metallothionen-2, Interleukin-2, metallothionen-1, ICAM-1, multi drug resistant Protein and Beta-actin.

When considered together, the references of *Debouck,* (teaching the use of arrays as mining tools to identify genes of interest), *Lillicrap* (suggesting that the canine gene RPE6 could be placed on an array), and *Aguirre* (teaching canine expression levels for factor VIII can be monitored), *Pirson (dislosing sequence for c-myc), Yokota (disclosing sequence for c-erbB2), Nakamura (disclosing sequence for catalse), Van Leeuwen*

(disclosing sequence for p53), Kobayashi (disclosing sequence for metallothionen-2), Somberg (disclosing sequence for Interleukin-2), Kobayashi (disclosing sequence for metallothionen-1), Manning (disclosing sequence for ICAM-1), Puel (disclosing sequence for multi drug resistant Protein), Ortiz-Garcia (disclosing sequence for Beta-actin) do not provide a teaching, suggestion, or motivation to make the combination of the toxicologically responsive sequences SEQ ID Nos.: 115-124 on a toxicologically responsive array. In contrast, Applicant has identified genes having the characteristic of interest (toxicologically responsive) for a panel of drugs. When the sequences (corresponding to at least a portion of the identified gene) are placed on array along with other toxicologically responsive sequences having toxicologically relevant characteristics, an array of toxicological responsive elements for early identification of compounds in canines is created. The genes were selected based upon toxicological responsiveness to at least one drug in Table 10.

B. THERE IS NO MOTIVATION, SUGGESTION, OR TEACHING OF THE DESIRABILITY OF MAKING THE SPECIFIC COMBINATION THAT WAS MADE BY THE APPLICANT

Identification in the prior art of each individual part claimed in a patent is insufficient to defeat patentability of

the whole claimed invention. Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant. In an obviousness determination, the factual question of motivation to combine prior art is material to patentability, and cannot be resolved on subjective belief and unknown authority. In re Lee 1277 F.3d 1338, 1345, 61 U.S.P.Q.2d 1430, 1433-1434 (Fed. Cir. 2002). An Examiner can satisfy the burden of showing obviousness of the combination only by showing some objective teaching in the prior art. Id. at 1344, 61 U.S.P.Q.2d at 1433-1434 ("The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record.").

The mere publication of the gene sequence for c-myc, c-erbB2, catalse, p53, metallothionen-2, Interleukin-2, metallothionen-1, ICAM-1, by itself suggests nothing about the toxic response characteristics of these 10 genes. At best, the publication of the sequences creates an invitation to experiment in order to determine whether the genes are immunologically responsive, toxicologically responsive, differentially expressed during an organism's development or constitutively active. The answer to these questions cannot be addressed by examining the molecular sequence of the gene. Rather the answer is derived

from a thorough analysis of the responsiveness of the gene to various insults, toxic compounds delivered at different dosages and at different time points. This information could not have been and is not derived from the combination of references that the Examiner cites in her 103(a) rejection.

Neither *Debouck* nor *Aguirre* nor *Lillicrap* suggests or hints that the genes coding for c-myc, c-erbB2, catalse, p53, metallothionen-2, Interleukin-2, metallothionen-1, ICAM-1, multi drug resistant protein and Beta-actin are responsive to toxicological compounds. It is only in light of Applicant's specification that one would be motivated to choose from the pool of thousands of genes that exist, these ten (10) genes, the unique combination as disclosed in claims 48-53. (See Table 11, Figure 2, pg, 17, ¶ 70; pg. 18, ¶73; and pg. 19, ¶75). It is only in light of Applicant's own specification that these genes are shown to exhibit toxicologically responsive characteristics that would motivate one to place partial gene sequences derived therefrom on an array for toxicological measurement. (Figure 2, Table 11 and Table 9).

Applicant discloses that the combination of SEQ ID Nos.: 115-124 provides toxicologically relevant characteristics for measuring toxicological responsiveness across multiple compounds shown to be toxic to canines (for example the canine kidney, spleen, testes, heart, thymus and liver). (pg. 19, ¶ 75,).

Table 11 and Figure 2 illustrates the differential gene expression for SEQ ID Nos.:116-118, 120, and 123 in response to dosing with acetaminophen, amphoteracin, erythromycin, estradiol, methotrexate and cadmium chloride which are provided as examples of the compounds tested from Table 10. Applicant has identified that SEQ ID No.: 116-118, 120 and 123 measure the differential expression of c-erbB2, catalase, p53, metallothionen-1, multi-drug resistant protein, respectively, across a broad range of drugs at concentrations toxic to canines organs such as liver and kidney (see Table 11, Figure 2 and pg 19, ¶ 75).

The Examiner has failed to establish a *prima facie* case of obviousness since there is no objective reasoning for finding motivation to combine the teachings of *Debouck, Lillicrap, Aguirre, Pirson, Yokota, Nakamura, Van Leeuwen, Kobayashi, Somberg, Kobayashi, Manning, Puel,* and *Ortiz-Garcia* other than the applicant's own record. There is no expectation or suggestion that any one of the ten (10) genes described by the references in question are toxicologically responsive to any toxic compound. Therefore, no one would be motivated to combine the specific 10 sequences disclosed in claim 47 as a composition on a toxicologically responsive array or in combination with the other 374 sequences disclosed as toxicologically responsive.

C. THE EXAMINER IS ENGAGED IN IMPERMISSIBLE HINDSIGHT RECONSTRUCTION

The Examiner selected the references based upon Applicant's disclosure which identifies partial gene sequences (SEQ ID Nos.: 115-179, 182, 185, 188, 191, 194, 197, 200, 203, 206, 209, 212, 213-328 and 330-384) from canine genes that respond to toxic compounds before the compound produces pathological damage to the system. (pg. 21,¶ 81,). Applicant describes the differential expression for these genes in Table 11 for a list of exemplary toxic compounds and also in Table 9 and figure 2. The sequences on the array are shown to hybridize to at least a portion of a gene that is differentially expressed as a result of dosing canines with toxic compounds (pg. 22, ¶ 82)).

Neither *Debouck,* nor *Lillicrap* nor *Aguirre* provide any suggestion or motivation for testing the genes disclosed by *Pirson, Yokota, Nakmura, Van Leeuwen, Kobayashi, Somber, Kobayashi, Manning, Puel, and Ortiz-Garcia* for their toxicity responsiveness to different dosings for toxic compounds in general or the toxic compounds listed in Table 10. Neither *Debouck* nor *Lillicrap* nor *Aguirre* provides any suggestion or motivation for an array having toxicity responsive characteristics of SEQ. ID. Nos.: 115-124 as elements thereon for early detection of toxicity screening induced by compounds of

interest in canines.

Applicant's disclosure identifies canine sequences which hybridize to genes identified as early indicators of compound toxicity in canines (producing organ damage at later time points as a result of dosing the animal with toxic compounds or producing changes in blood chemistry indicative of toxicity). These sequences include SEQ ID Nos.: 115-124. Further Applicant's disclosure identifies sequences which hybridize to at least a part of a gene which is an early indicator of canine organ damage resulting from dosing the animal with toxic compounds and include SEQ. ID Nos.: 125-179, 182, 185, 188, 191, 194, 197, 200, 203, 206, 209, 212, 213-328, and 330-384 and complements thereof. SEQ. ID Nos.: 125-179, 182, 185, 188, 191, 194, 197, 200, 203, 206, 209, 212, 213-328, and 330-384 hybridize to genes that are differentially expressed in response to at least one of the compounds that are listed in table 10. In the absence of this information there is no motivation to make the combination of sequences to create a toxicologically responsive array as recited in claims 47-54.

Applicant's disclosure identifies the toxicologically relevant canine genes as a result of screening a large candidate array for genes whose differential expression is affected by dosing toxic compounds in canines. Selection of partial gene sequences for placement as an element on the array depended on

the partial gene sequence corresponding to at least a portion of a gene whose differential expression changed in response to toxic compound dosing in canines for one or more drugs and wherein the change in expression was statistically significant (See Table 11). In the absence of Applicant's data identifying which genes are toxicologically responsive and statistically relevant, the array would be composed of randomly selected partial gene sequences whose combination would not be toxicologically relevant for early detection of compound toxicity in canines.

Claim 45 is currently pending and depends from claim 47. Claim 45 is non-obvious for at least the reasons as stated above for claim 47.

Claim 46 is currently pending and depends from claim 47. Claim 46 is non-obvious for at least the reasons as stated above for claim 47.

II. THE COMBINATION OF NUCLEIC ACIDS SEQUENCES IN CLAIMS 48-54 CONTAIN A NOVEL SEQUENCE AND SHOULD RENDER THE ENTIRE COMBINATION ALLOWABLE

In a telephone interview with Examiner Goldberg on Tuesday May 11, 2004, the Examiner stated that she would be willing to examine one additional nucleotide sequence if Applicant clearly pointed out which sequence was novel and where in the

specification the Examiner should look to find information about the sequence.

Applicant accepts the Examiner's kind offer and identifies SEQ ID. No.: 329 in claim 48, 51, 52, 53, and 54 as the novel sequence to be examined.

SEQ ID No.: 329 hybridizes to at least a portion of a gene that is toxicologically responsive to toxic compounds administered to canines as disclosed in Table 9 (SEQ ID No.: 329 is listed as the first item in Table 9 and is alternatively known as CTP1D in Table 8. CTPD1 is the first item in Table 8 and is cross referenced to SEQ ID No.: 329).

Further, the combination of SEQ ID No.: 329, in combination with SEQ ID No.: 115-124 is non-obvious especially since SEQ ID No.: 329 has no known homology match in GenBank. Further still, SEQ ID. No.: 329 hybridizes to at least a portion of a gene that is toxicologically responsive to compounds that are toxic to canines as disclosed in Table 9 (for example aspirin, caffeine and etoposide). Further still, the addition of SEQ ID No.: 329 to the combination of 115-124 is a further limitation to a combination that is non-obvious.

Claim 48 is new and depends from claim 47 and is non-obvious for at least the reasons stated above and for the additional reason that the array further comprises at least one novel sequence (SEQ ID 329). The presence on one novel and non-obvious

sequence within the combination should render the entire combination allowable (See MPEP 803.04)

Claim 49 is new and recites an array comprising the plurality of partial gene sequences from toxicologically relevant canine genes. The genes having the characteristic of being derived from toxiciologically relevant canine genes as disclosed in the specification at pg. 20, ¶ 77.

Claim 50 is new and recites the combination of partial gene sequences from toxicologically relevant canine genes. This combination is non-obvious for at least the reasons as stated above.

Claim 51 is new and recites novel SEQ ID No.: 329 in the combination. The presence on one novel and non-obvious sequence within the combination should render the entire combination allowable (See MPEP 803.04).

Claim 52 is new and is non-obvious in light of the references cited since the combination includes the novel SEQ ID No.: 329 in addition to SEQ ID No.: 116-118, 121, and 123. The presence on one novel and non-obvious sequence within the combination should render the entire combination allowable (See MPEP 803.04)

Claim 53 is new and depends from Claim 52. Claim 53 is non-obvious since it depends from claim 52 which contains at least one novel gene sequence (SEQ ID No.: 329) in combination with

others. The presence on one novel and non-obvious sequence within the combination should render the entire combination allowable (See MPEP 803.04). Claim 53 further adds the additional limitations of SEQ ID. Nos.: 115, 119, 120, 124-179, 182, 185, 188, 191, 194, 197, 200, 203, 206, 209, 212, 213-328, and 330-384.

Claim 54 is new and recites a method of using the array as recited in claim 53. Claim 54 limits the method to the specific array as recited in claim 53 for "contacting the nucleic acids of the sample with an *array comprising* the plurality of SEQ IDs of claim 53 under conditions to form one or more hybridization complexes" (lines 4-6). Since Claim 53 contains at least one novel and non-obvious gene sequence (SEQ ID. No.: 329) in the combination, and the array of claim 53 is a further limitation of claim 54, the combination should render the entire combination of elements allowable.

Accordingly, Applicant respectfully submits that the prior art does not establish a *prima facie* case of obviousness with respect to claims 47-54.

II. CLOSING

In view of the above, Applicant respectfully submits that independent claims 47, 49, 50,52 and 54 are patentable over the prior art. Applicant further submits that dependent claims 45-46, 48, 50, 51 and 53 are patentable, at least as being dependent

from patentable independent claims, and are further patentable due to the additional limitations recited therein.

For the above reasons, Applicant respectfully submits that the application is in condition for allowance with claims 45-54. If there remain any issues that may be disposed of via a telephonic interview, the Examiner is kindly invited to contact the undersigned at the local exchange given below.

The Director of the Patent and Trademark Office is authorized to charge any necessary fees, and conversely, deposit any credit balance, to Deposit Account No. 18-1579.

Respectfully submitted,
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